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The Insults of Illicit Drug Use on Male Fertility

Review

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ABSTRACT: One-third of infertile couples may have a male factor present. Illicit drug use can be an important cause of male factor infertility and includes use of anabolic-androgenic steroids, marijuana, opioid narcotics, cocaine, and methamphetamines. The use of these illicit drugs is common in the United States, with a yearly prevalence rate for any drug consistently higher in males compared with females. We aim to provide a review of recent literature on the prevalence and effects of illicit drug use on male fertility and to aid health professionals when counseling infertile men whose social history suggests illicit drug use. Anabolic-androgenic steroids, marijuana, cocaine, methamphetamines, and opioid narcotics all negatively impact male fertility, and adverse effects have been reported on the hypothalamic-pituitary-testicular axis, sperm function, and testicular structure. The use of illicit drugs is prevalent in our society and likely adversely impacting the fertility of men who abuse drugs.

Key words: Male infertility, subfertility, male factor infertility, epidemiology, illicit drugs, substance abuse, anabolic-androgenic steroids, marijuana, methamphetamines, cocaine, opioid narcotics, human and animal studies.

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Exposures to certain drugs and toxins may play a role in male infertility. Recreational use of illicit drugs is an important consideration when assessing the etiology of male infertility. Yearly, the National Survey of Drug Use and Health (NSDUH) conducted by the Department of Health and Human Services (Substance Abuse and Mental Health Services Administration [SAMHSA], 2010) estimates illicit drug use in the United States for the noninstitutionalized population ages 12 years or older. The NSDUH provides strong evidence that illicit drug use is prevalent among men who are of the ages likely to be seeking infertility treatment. Among men in the age groupings of 26–34 years, 35–49 years, and 50 years and older, past year use of any illicit drug surveyed was 24.6%, 14.5%, and 7.8%, respectively, and past month use was 14.3%, 8.7%, and 5.0%, respectively. The illicit drugs that have been found to adversely impact male fertility are marijuana, opioid narcotics, methamphetamines, cocaine, and anabolic-androgenic steroids (AAS). We aim to provide an understanding of the use prevalence of these illicit drugs and their adverse effects on male fertility.

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Methods

A PubMed database search was conducted between April 2010 and December 2010 for articles addressing the effects of illicit drug use on male fertility using combinations of the following key words: male infertility, subfertility, male factor infertility, illicit drugs, recreational drugs, substance abuse, anabolic-androgenic steroids, marijuana, cannabis, amphetamines, methamphetamines, Ecstasy, cocaine, opioids, narcotics, prescription analgesics, epidemiology, human studies, and animal studies. When evaluating studies to include in this review, we aimed to include studies of historical importance and recent publications, and to focus on human studies. Only in cases where human studies were not available or were severely limited were animal studies used to estimate the impact of a drug on male fertility. Drug use statistics were calculated from data reported in the 2009 NSDUH conducted by the US Department of Health and Human Services SAMHSA (SAMHSA, 2010). Statistics on specific drugs for males in age ranges of 26–34 years, 35–49 years, and 50 years and older were calculated using the SAMHSA online tool, which allows survey analysis from the 2009 archives. These age ranges were chosen on the basis that they are the most relevant age ranges of men who may be seeking infertility treatment. The NSDUH specifically defined what constitutes drug use. Marijuana use was defined as the use of marijuana or hashish. Nonmedical use of prescription pain relievers was identified by the nonmedical use of at least one

"pain-relieving" medication without a prescription belonging to the respondent, or use that occurred simply for the experience or feeling the drug caused. Pain relievers were defined as medications in the following categories: Darvocet, Darvon, or Tylenol with Codeine; Percocet, Percodan, or Tylox; Vicodin, Lortab, or Lorcet/Lorcet Plus; Codeine; Demerol; Dilaudid; Fioricet; Fiorinal; Hydrocodone; Methadone; Morphine; Oxycontin; Phenaphen with Codeine; Propoxyphene; SK-65; Stadol; Talacen; Talwin; Talwin NX; Tramadol; and Ultram. Cocaine use was defined as use of cocaine in any form, including crack and powder. Methamphetamine use was defined as use of crystal meth, ice, speed, crank, and nonmedical use of Desoxyn or Methederine. This review focuses on use of marijuana, nonmedical use of methamphetamines and Ecstasy (3,4-methylenedioxy-*N*-methylamphetamine [MDMA]), nonmedical use of prescription opioid narcotics, cocaine, and AAS, because these illicit drugs can contribute to male factor infertility. AAS use is not collected by the NSDUH survey, and thus AAS use statistics were taken from the 2009 Monitoring the Future (MTF) study. This study is a yearly study of illicit drug use trends among secondary school students, college students, and adults through age 50 years in the United States. This study is conducted annually by the Institute for Social Research at the University of Michigan through grants awarded by the National Institute on Drug Abuse (Johnston et al, 2009).

Results and Discussion

Marijuana—Marijuana has the highest use rate among all illicit drugs surveyed by the NSDUH in 2009, with 20.1%, 10.6%, and 5.3% of males ages 26–34 years, 35–49 years, and 50 years and older, respectively, reporting use of marijuana in the past year, and 11.6%, 6.2%, and 3.4% of males in these respective age categories reporting use within the past 30 days (Table 1). The rate of past year marijuana use between 2008 and 2009 among males 26 years and older increased from 8.8% to 10.0%, respectively (SAMHSA, 2009, 2010).

Impact on Male Fertility—Marijuana, consisting of dried leaves and flowers from the marijuana plant (*Cannabis sativa*), is smoked to release the psychoactive cannabinoid compound called delta-9-tetrahydrocannabinol (THC). In the 1990s, it was found that cannabinoid compounds are also naturally synthesized by the human body from fatty acid derivatives, termed *endogenous cannabinoids* or *endocannabinoids* (Devane et al, 1992; Felder et al, 1992). The two most well-studied endocannabinoids are arachidonoylethanolamine, also known as anandamide, and 2-arachidonoylglycerol. Endocannabinoids may modulate several pathophysiologic processes, including neuropathic pain, mood disorders, movement disorders such as Parkinson disease and Huntington disease, disease processes such as cancer, atherosclerosis, and obesity, as well as reproductive functions (Schuel et al, 2002; Pacher

Table 1. *Illicit drug use among males estimated from the 2009 National Survey on Drug Use and Health*

Illicit Drug	Ages 26–34 y (%)	Ages 35–49 y (%)	Ages 50 y or Older (%)
All illicit drugs			
Past year	24.6	14.5	7.8
Past month	14.3	8.7	5.0
Anabolic-androgenic steroids	Ages 19–30 y = 0.7%	...	...
Marijuana			
Used within past year	20.1	10.6	5.3
Current user	11.6	6.2	3.4
Cocaine			
Current user	1.5	0.9	0.6
Used within past year	4.2	2.2	1.0
Methamphetamines			
Ecstasy (MDMA)			
Current user	0.5	0.1	0.0
Used within past year	2.0	0.6	0.0
Methamphetamines			
Current user	0.4	0.5	0.1
Used within past year	0.7	0.9	0.1
Prescription pain relievers used nonmedically			
Used in past year	8.3	4.8	2.4
Used in past month	3.3	2.5	1.0

Abbreviation: MDMA, 3,4-methylenedioxy-*N*-methylamphetamine.

et al, 2006). Endocannabinoid receptors are found on numerous cells, including neurons, immune cells, and vascular endothelial and muscle cells (Howlett et al, 2002), as well as on human testes (Munro et al, 1993; Schuel et al, 2002) and the head and middle pieces of sperm (Rossato et al, 2005).

Human studies consistently conclude that THC negatively affects male reproductive physiology (Table 2). There are observed disruptions in the hypothalamic-pituitary-testicular axis, with marijuana users having decreased levels of luteinizing hormone (LH; Cone et al, 1986; Vescovi et al, 1992). When investigating testosterone levels, chronic and exclusive marijuana smokers were found to have significantly lower plasma testosterone compared with age-matched controls who had never used marijuana, and the reduction was dose dependent (Kolodny et al, 1974). More than one-third of the chronic exclusive marijuana smokers studied by Kolodny et al (1974) had oligospermia, likely resulting from decreased LH levels, which reduce testosterone secretion, which in turn reduces spermatogenesis. Activation of the endocannabinoid receptors on sperm by either anandamide or THC has also been reported to reduce sperm motility in a dose-dependent manner and inhibit the capacitation-induced acrosomal reaction (Schuel et al, 2002; Rossato et al, 2005; Whan et al, 2006). However, Schuel et al (2002) found a biphasic effect at different concentrations of anandamide. Sperm were inhibited at higher levels but hyperactivated at lower levels of anandamide. Reductions in sperm motility may be due to an anandamide- or THC-induced inhibition of sperm mitochondrial activity, which initiates sperm apoptosis (Rossato et al, 2005; Badawy et al, 2009). Interestingly, when THC was added to neat sperm, mitochondrial respiration was less affected, suggesting that cells that secrete components of seminal fluid may also secrete unidentified factors that protect against THC's inhibitory actions toward sperm (Badawy et al, 2009).

In addition, normal operation of the endocannabinoid signaling systems requires rapid release and rapid removal of endocannabinoids (Piomelli et al, 1998). THC has a long half-life ranging from 24 to 36 hours because it is lipid soluble, which allows it to enter fatty tissue that then acts as a reservoir to slowly release THC back into the blood. Studies with rats have shown that after THC administration with approximately 0.06% and 0.02% of the administered dose concentrates in brain and testis, respectively (Nahas et al, 2002). The presence of such doses of THC in the testis may overstimulate endocannabinoid receptors and contribute to alter sperm motility and male infertility.

Prescription Opioid Narcotics—Nonmedical use of prescription opioid narcotics, such as Vicodin (hydrocodone/acetaminophen), Darvocet-N (propoxyphene/acetaminophen), and oxycodone have the second highest abuse rate among illicit drugs after marijuana, with 8.3%, 4.8%, and 2.4% of males ages 26–34 years, 35–49 years, and 50 years and older, respectively, reporting nonmedical use of prescription pain medication in the past year, and 3.3%, 2.5%, and 1.0% of men in these respective age groups reporting current nonmedical use of narcotics (Table 1; SAMHSA, 2010).

Impact on Male Fertility—Prescription narcotics result in suppression of the hypothalamic-pituitary axis through opioid-induced inhibition of gonadotropin-releasing hormone (GnRH) pulse patterns, which leads to suppression of LH release and subsequent decrease in testosterone levels and spermatogenesis (Table 3). Testosterone deficiency was documented more than three decades ago in patients treated for heroin addiction with methadone (Azizi et al, 1973; Cicero et al, 1975).

Intravenous administration of various opioid drugs to healthy male participants led to decreases in serum LH due to suppression of LH pulse frequency, with no significant change in follicle-stimulating hormone (FSH) levels (Delitala et al, 1983; Pende et al, 1986). LH pulse frequency inhibition can be overcome by opioid antagonists, such as naltrexone (Ellingboe et al, 1982; Veldhuis et al, 1984).

In studies examining endocrine function in men chronically using intrathecal (average dose of morphine, 4.8 mg), oral, and transdermal opioids to control intractable nonmalignant pain, nearly all men reported symptoms of hypogonadism, including decreased libido or impotency and significantly lower testosterone and LH levels, compared with men not receiving opioid treatment (Abs et al, 2000). Daniell (2002) found that decreases in testosterone and LH did not differ between men consuming different forms of narcotics in comparable doses and were unrelated to the frequency of opioid use and other characteristics such as smoking, alcohol use, height, weight, and body mass index. However, a more recent study suggests that different narcotics may have different impacts on male fertility, because men using buprenorphine, a partial-opioid agonist for opioid dependence, reported significantly higher testosterone levels and lower frequency of sexual dysfunction than men receiving treatment with methadone (Bliesener et al, 2005).

Vuong et al (2010) did an extensive literature review addressing the effects of opioids on the endocrine system and recommend that sex hormone–binding globulin, which is elevated in men taking opioids, as well as free and total testosterone, which are typically decreased, be measured when investigating the prevalence of hypogonadism in men taking opioids. Measuring these parameters would reduce the likelihood that men with total

Table 2. *Effects of marijuana on select aspects of male fertility*[a]

	Effects of Marijuana	Case Description	Dosing	Type of Study	References
Hormone profiles					
FSH LH Serum testosterone	↔ ↓ ↔	Human, male 4 "frequent" marijuana smokers	Combinations of 1 or 2 cigarettes consisting of 2.8% THC or placebo smoked consecutively for 3 d	Human, random crossover	Cone et al, 1986[b]
LH	↓	Human, male 10 chronic marijuana smokers ages 19–20 y with mean length of marijuana exposure of more than 12 mo	1 g of marijuana containing 1.83% THC once every day	Matched case-control, human study	Vescovi et al, 1992[c]
Plasma testosterone	↓	Human, 20 male chronic marijuana users, smoking marijuana at least 4 d for 6 mo	Not reported	. . .	Kolodny et al, 1974[d]
LH	↓	4 "frequent marijuana smokers" ages 22, 26, 33, and 54 y	2 cigarettes consisting of 2.8% THC, 1 THC cigarette and 1 placebo, or 2 placebos, smoked each for 3 consecutive days	Human, random crossover	Cone et al, 1986[b]
LH	↓; chronic treatment with marijuana suppresses basal and stimulated values of LH	. . .	. . .	. . .	Vescovi et al, 1992[c]
Serum testosterone, free and plasma	↔	. . .	. . .	. . .	Cone et al, 1986[b]
Plasma testosterone	↓	20 men, chronic marijuana smokers smoking marijuana at least 4 d for 6 mo	Not reported	Human, case-control	Kolodny et al, 1974[d]
Semen profiles					
Sperm motility	↓	5 men	Sperm motility and viability assessed by light microscopy after sperm incubation at various concentrations of anandamide at different exposure durations. Acrosomal reaction induced by calcium ionophore ionomycin	In vitro, human semen samples	Rossato et al, 2005[e]; Whan et al, 2006[f]
	↓	78 men, semen samples ages 26–42 y	THC therapeutic (0.032 μM) and recreational (0.32 and 4.8 μM) plasma levels, 2 fractions of sperm tested, 90% (best fertilizing potential) and 45% (poor fertilizing potential)	In vitro, human sperm	Whan et al, 2006[f]

Table 2. *Continued*

	Effects of Marijuana	Case Description	Dosing	Type of Study	References
Hyperactivated motility	Biphasic effects between 1 and 6 h of incubation	...	Anandamide inhibited at 2.5 nM, stimulated at 0.25 nM	In vitro human sperm	Schuel et al, 2002[g]
Functional profiles					
Capacitation-induced acrosomal reaction	Impaired	...	Anandamide doses >1.0 μM	In vitro, human semen samples	Rossato et al, 2005[e]
	Inhibited	...	THC and anandamide	In vitro human sperm	Schuel et al, 2002[g]
Viability	↓	...	Anandamide doses >1.0 μM	In vitro, human semen samples	Rossato et al, 2005[e]
	↔	...	Anandamide and THC	In vitro human sperm	Schuel et al, 2002[g]
Mitochondrial activity	Inhibits in a dose-dependent manner	...	...	In vitro, human semen samples	Rossato et al, 2005[e]
Sperm mitochondrial oxygen consumption	Inhibited	41 men	THC (delta-9 and delta-8)	In vitro, human sperm and human seminal fluid	Badawy et al, 2009[h]

Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone; THC, delta-9-tetrahydrocannabinol.

[a] Arrows indicate changes in values: ↓, decrease; ↔, no change.

[b] Participants: 4 "frequent" marijuana smokers, males; dose: combinations of 1 or 2 cigarettes consisting of 2.8% THC or placebo smoked consecutively for 3 days.

[c] Participants: 10 chronic marijuana smokers, male, mean duration of marijuana smoked is more than 12 months; dose: 1 g of marijuana containing 1.83% THC once every day.

[d] Participants: 20 chronic marijuana smokers, male; exposure: smoked marijuana at least 4 days per week for 6 months.

[e] Participants: 5 men. In vitro, human sperm incubation at varying concentrations of anandamide and varying exposure durations.

[f] Participants: 78 men, in vitro, human sperm. Exposure: THC therapeutic (0.032 μM) and recreational (0.32 and 4.8 μM) plasma levels, two fractions of sperm tested, 90% (best fertilizing potential) and 45% (poor fertilizing potential).

[g] Participants: In vitro human sperm. Product: anandamide and THC.

[h] Participants: 41 men, in vitro human sperm and seminal fluid. Exposure: THC (delta-9 and delta-8).

testosterone levels at or just above the lower limit of normal would be classified as eugonadal when they are instead hypogonadal (Vuong et al, 2010).

Giving exogenous testosterone is a potential option for countering opioid-induced hypogonadism. Abs et al (2000) found that androgen supplements helped improve sexual function in most patients on chronic intrathecal morphine. In an open-label study of men on chronic opioids with hypogonadism, treatment with testosterone patch therapy at a low dose of 7.5 mg/d resulted in significantly elevated free and total testosterone levels from baseline as well as improved sexual function and mood (Daniell et al, 2006). However, administration of exogenous testosterone does have the potential to inhibit spermatogenesis. Studies investigating testosterone administration for male contraception have found that exogenous testosterone may cause a negative feedback mechanism on the hypothalamic-pituitary-testicular axis, suppress LH and FSH, deplete intratesticular testosterone, and lead to azoospermia. However, such suppressive effects are dependent on testosterone dose and method of delivery, with transdermal administration alone being the least likely to suppress spermatogenesis (Hair et al, 2001; Gonzalo et al, 2002; Nieschlag, 2010). It is important to highlight the limitations of the literature, whereby much higher doses of multiple drugs used by abusers make comparisons to medical treatment effects difficult.

Cocaine—NSDUH estimates in 2009 report prevalence use of cocaine for males in the age groups 26–34 years, 35–49 years, and 50 years and older at 4.2%, 2.2%, and 1.0% for past year, and 1.5%, 0.9%, and 0.6% for current users, respectively (Table 1; SAMHSA, 2010). Cocaine use is unique among illicit drugs in that prevalence rates remain steady with age, whereas active use of all other drugs declines throughout the 20s (Johnston et al, 2009). Cocaine use began to decline in all age groups in 2008 (Johnston et al, 2009), and for all age groups, including men and women, the annual number of cocaine initiates declined from 1.0 million in 2002 to 617,000 in 2009. The number of initiates of crack cocaine declined during this period as well, from 337,000 to 94,000. In 2008, the lifetime prevalence of cocaine use among 50-year-olds reached 40% (Johnston et al, 2009).

Table 3. *Effects of prescription opioid narcotics on select aspects of male fertility*

Hormone Profiles	Effects of Opioid	Species and No. of Participants	Dosing	Type of Study	Product	References
LH	↓	Human, 6	Morphine (10 mg), methadone (10 mg), pentazocine (30 mg), nalorphine (10 mg), and 0.25 mg of the metenkephalin analog, DAMME	Human, males	...	Delitala et al, 1983
LH	↓	24 males	...	Human	...	Pende et al, 1986
Decreased testosterone. Decreased libido, impotency. Decreased serum LH, no change FSH.	...	29 males	Intrathecal opioids, mean daily dose morphine 4.8 ± 3.2 mg; mean duration of treatment was more than 24 months	Human, cross-sectional	...	Abs et al, 2000
Decreased testosterone	...	12 men	Oral or transdermal, all doses converted to morphine equivalent dose	Human, cross-sectional	...	Fraser et al, 2009
Decreased free testosterone, total testosterone, dihydrotestosterone	...	54, community dwelling	Oral opioids, at least 20 mg hydrocodone for 2 wk or more, all doses converted to methadone equivalents	Human, cross-sectional	...	Daniell, 2002

Abbreviations: DAMME, D-Ala(2), MePhe(4), Met(0)-01-enkephalin; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Impact on Male Fertility—Evidence consistently demonstrates the teratogenic effects of cocaine use on fetal development when abused by women during pregnancy, but studies on the impact of cocaine on male fertility are lacking because of the inability to prospectively study effects. Studies are further complicated by probable concurrent use of other illicit substances. However, Bracken et al (1990) reported some interesting findings through interviewing male patients who presented to a Yale infertility clinic. Men with sperm counts less than 20 million per milliliter were two times more likely to have used cocaine within the past 2 years than men who had not used cocaine (Table 4). Also, men with a 5-year or greater history of cocaine use were two times more likely to have low sperm motility (Bracken et al, 1990).

In addition to the observations made by Bracken et al (1990), an understanding of the specific effects of cocaine on male fertility is best estimated through animal studies. Rats that were chronically exposed to cocaine at a level comparable to that of a heavy cocaine user (15 mg/kg body weight) had respective pregnancy rates of 33% and 50% for 100 and 150 days of cocaine exposure, compared with 86% and 100% of controls, respectively, for the same exposure duration (George et al, 1996). Testicular tissue receptors in rats have also been found to bind cocaine in a saturable and specific manner (Li et al, 1997). Rodriguez et al (1992) reported that cocaine exposure to rats in low doses (0.5 mg/kg body weight) and high doses (10 mg/kg body weight) resulted in acute negative effects on spermatogenesis, and they also observed that 50%–60% of seminiferous tubules were abnormal, with cellular degeneration, cell sloughing, or abnormal cell structures. Ultrastructural examination of the seminiferous epithelium (spermatogonia, spermatids, and Sertoli cells) revealed vacuoles, abundant lipid droplets, and giant mitochondria (Rodriguez et al, 1992). Chronic cocaine administration for 90 days to peripubertal rats induced apoptosis in 25% of germinal epithelium of spermatocytes and spermatogonia with DNA displaying a clear ladder pattern (Li et al, 1999a). Li et al (1999b) also report that blood flow to rat testes is reduced after subcutaneous injections of high-dose cocaine (30 mg/kg body weight), with vasoconstriction found to be most prominent after 15 minutes, persisting up to 60 minutes, and finally restored to baseline by 4.5 hours. They conclude that adverse effects of cocaine on the testes may be in part due to ischemic and postischemic reperfusion injury.

Methamphetamines and Ecstasy—Methamphetamine use by men is quite small, with the NSDUH reporting the highest yearly prevalence rate at 1.1% among males in the age group 19–25 years. For males ages 26–34 years, 35–49 years, and 50 years and older, methamphetamine use is 0.7%, 0.9%, and 0.1% for past year use, and 0.4%, 0.5%, and 0.1% for current users of methamphetamine in these age groupings, respectively (Table 1; Johnston et al, 2009). The prevalence of Ecstasy (MDMA) use is also highest in the male age group 19–25 years at 5.2%, and it drops considerably for older age groups. Prevalence of Ecstasy use among males ages 26–34 years and 35–49 years for past year use and current use is at 0.5% and 0.1%, respectively, and is

Table 4. *Effects of cocaine on select aspects of male fertility*

	Species and No. Involved in Study	Effect of Drug	No. of Participants	Product and Dosing, Duration	Details on Study Participants	References
Hormone profile						
Testosterone	Rat	Increased at low dose, no change at high dose compared with controls	12 in each high and low dose	Cocaine hydrochloride, subcutaneous injection 0.5 and 10 g/kg cocaine hourly over 5 h	30 male Wistar rats, 12 in high dose, 12 in low dose, 6 controls	Rodriguez et al, 1992
LH	Rat	No changes	...	...	...	Rodriguez et al, 1992
Semen analysis						
Sperm concentration	Human, 1309 males seeking infertility diagnosis	Reduced sperm count ($<20 \times 10^6$) if used cocaine within 2 y of analysis	1309 males	Survey assessing history of cocaine use	Cross-sectional, nested case-cohort Men seeking an infertility diagnosis	Bracken et al, 1990
Sperm motility	...	Reduced if cocaine used for 5 y or more duration at time of analysis	...	...	...	Bracken et al, 1990
Abnormal sperm morphology	Rat, number not specified	Increase apoptosis in spermatocytes and spermatogonia in testicular epithelium; clear ladder pattern in DNA	Number not specified	Subcutaneous injection cocaine hydrochloride (15 mg/kg) for 90d	Animal, Sprague-Dawley rats, case-control	Li et al, 1999a
Testicular changes						
Seminiferous tubules	Decline in normal tubules, cellular degeneration, sloughing, abnormal cells. Diameter and volume decreased.	Evidence of vacuoles, abundant lipid droplets, and giant mitochondria in spermatogonia, spermatids, and Sertoli cells	30 Male Wistar rats, 12 in high dose, 12 in low dose, 6 controls	Hourly subcutaneous injection 0.5 and 10 g/kg cocaine hydrochloride over 5 h	...	Rodriguez et al, 1992
	...	Reduced mean diameter of seminiferous tubules, reduced thickness of germinal epithelium, degenerating cells more numerous, reduced number of spermatids	...	...	...	George et al, 1996
Testicular blood flow	...	Reduced, vasoconstriction persisted up to 60 minutes	Number not speciried	Subcutaneous cocaine, 30mg/kg body weight	Animal, Sprague-Dawley rats, case-control	Li et al, 1999a

Table 4. *Continued*

	Species and No. Involved in Study	Effect of Drug	No. of Participants	Product and Dosing, Duration	Details on Study Participants	References
Functional properties	Animal, in vitro, case-control	Reduced pregnancy rate	66 male Sprague-Dawley rats	Subcutaneous injection cocaine hydrochloride (15 mg/kg), daily or twice weekly	...	George et al, 1996

nonexistent for men 50 years and older, according to the NSDUH.

Impact on Male Fertility—The impact of methamphetamine use on male fertility has not been rigorously explored. Physiologically, amphetamines and MDMA act upon the dopaminergic and serotoninergic systems, influencing the secretion of GnRH (Vitale et al, 1986). The studies of amphetamines and Ecstasy on male fertility are modeled through animal studies (Table 5). In vitro and in vivo male rat studies showed that a single injection of amphetamine led to decreased plasma testosterone in a dose-dependent manner (Tsai et al, 1996). Tsai et al (1996) hypothesize that amphetamines induce an increase in cAMP, which acts through protein kinase A to block transmission of the Ras signaling pathway, an important pathway for transmitting hormones (Marx, 1993) and perhaps also an important pathway for the release of testosterone by Leydig cells. Acute injection of methamphetamine at different doses (5, 10, or 15 mg/kg) induced apoptosis in seminiferous tubules in male mouse testis, and DNA ladders were found with the highest injected doses of 15 mg/kg (Table 5; Yamamoto et al, 2002). Animal studies evaluating the impact of Ecstasy on reproductive neuroendocrine function found MDMA suppressed GnRH and serum testosterone levels, which significantly altered the hypothalamic-pituitary-testicular axis (Dickerson et al, 2008). The authors report that they administered doses that were relevant to human intake but acknowledge that metabolism and secretion of MDMA vary between species (Easton and Marsden, 2006). When examining Ecstasy exposure, there was a significantly higher incidence of sperm DNA damage, tubular degeneration, and interstitial edema in testes, although at all doses tested, sperm motility and morphology were not affected (Table 5; Barenys et al, 2009).

Anabolic-Androgenic Steroids—AAS are cholesterol derivatives of testosterone with effects that are both anabolic and androgenic to build lean muscle and enhance masculinization (Kopera, 1985; Bhasin et al, 1996; Sheffield-Moore and Urban, 2004; Pope and Brower, 2009). Popular types of AAS are oral oxandrolone (Oxandrin), oral methandienone (Dianabol), injectable stanozolol (Winstrol-V), injectable nandrolone decanoate (Deca-Durabolin), and injectable boldenone undecylenate (Equipoise). Stereotypically, the AAS user is a weightlifter or competitive athlete who combines intensive power lifting with AAS in supraphysiologic doses to enhance performance. Professional and amateur athletic associations are intolerant of the use of performance-enhancing substances and subscribe to antidoping organizations, such as the US Anti-Doping Agency or the World Anti-Doping Agency (WADA), or have their own guidelines and protocols to prevent doping, as does the National Collegiate Athletic Association. These antidoping regulations deter the use of performance-enhancing drugs by athletes. However, at the same time, these regulations have pushed the design of sophisticated doping compounds undetectable by current laboratory testing techniques (Kayser et al, 2007). It should be emphasized that testosterone, which is available as a prescription medication as well as illicitly, is an AAS (WADA, 2011). Testosterone (T) coupled with epitestosterone (E) have been abused together to disguise T/E ratios in athletic antidoping systems (Saudan et al, 2006). Elevated T/E ratios have been recognized as a marker of AAS use in athletes. In addition to the athletes who currently are able to dope undetected, the use of performance-enhancing drugs by the general public is a concern, because the typical user of AAS is a ''regular Joe'' who desires a leaner, more muscular physique so he can emulate the media-perpetuated image of masculinity and fitness (Buckley et al, 1988; Parkinson and Evans, 2006; Cohen et al, 2007).

In 2001, the annual prevalence rate of AAS use in high school boys was estimated to be between 8% and 12% but has since declined to an annual prevalence rate of 3% (Johnson et al, 1989; Kanayama et al, 2009b). In males ages 19–30 years, the annual prevalence rate was 0.7% (Table 1; Johnston et al, 2009). However, the lifetime prevalence of AAS use in males is estimated to be between 3.0% and 4.2%, and of concern are case reports of individuals taking AAS who develop depressive withdrawal symptoms after discontinuing AAS, and may develop AAS dependence as a result. Although AAS dependence needs further study, possible hypotheses include psychologic dependence due to body image disorders such as ''muscle dysmorphia'' (Pope et al,

Table 5. *Effects of methamphetamines on select aspects of male fertility*[a]

	Effects of Methamphetamines	Type of Study	Product	No. of Participants	Dosing	References
Hormone profiles						
LH	↔	Animal, rat, in vitro and in vivo	Amphetamines	...	In vitro: 0.4 μg/mL/kg	Tsai et al, 1996
GnRH	↓	Animal, male rats, 5 acute, 9 chronic	MDMA	MDMA once at 3 mg/kg (mimic the "binge"). Chronic 5-d administration MDMA over 4 wk, ad lib administration averaging 4 mg/kg body weight.	...	Dickerson et al, 2008
Serum testosterone	↓	...	...	...	...	Tsai et al, 1996
	↓	...	...	...	...	Dickerson et al, 2008
Semen profiles						
Sperm morphology	↔	...	...	...	...	Barenys et al, 2009
Abnormal sperm DNA	DNA ladders	...	...	...	...	Barenys et al, 2009
	...	Mice	Methamphetamine, injected doses 1, 5, 10, and 15 mg/kg	...	...	Yamamoto et al, 2002
Sperm motility	↔	...	...	...	...	Barenys et al, 2009
Testicular changes						
Abnormalities in seminiferous tubules	Apoptotic tubules, interstitial edema	Male rats	Ecstasy, subcutaneous at 0.5 mg/kg, 5, 10, once per day, 3 consecutive d per week for 12 wk, simulating human weekend consumption			Barenys et al, 2009
	...	...	...	...	...	Yamamoto et al, 2002

Abbreviations: GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; MDMA, 3,4-methylenedioxy-*N*-methylamphetamine.

[a] Arrows indicate changes in values: ↓, decrease; ↔, no change.

Table 6. *Effects of anabolic-androgenic steroids (AAS) on select aspects of male fertility*[a]

	Effects of AAS	References
Hormone profiles		
FSH	↓	Torres-Calleja et al, 2001; Bonetti et al, 2008
LH	↓	Bonetti et al, 2008
	↔	Torres-Calleja et al, 2001
Serum testosterone	↓	Schurmeyer et al, 1984
	↔	Torres-Calleja et al, 2001; Bonetti et al, 2008
Serum hormone–binding globulin	↓	Bonetti et al, 2008
Semen profiles		
Azoospermia	Yes	Schurmeyer et al, 1984; Torres-Calleja et al, 2001
Oligospermia	Yes	Knuth et al, 1989; Torres-Calleja et al, 2001; Bonetti et al, 2008
Abnormal sperm morphology	Amorphous, changes in the head, defects of the center pieces	Knuth et al, 1989; Torres-Calleja et al, 2001
Sperm motility	↓	Knuth et al, 1989
	↔	Bonetti et al, 2008
Testicular changes		
Atrophy	Yes	Bonetti et al, 2008

Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone.

[a] Arrows indicate changes in values: ↓, decrease; ↔, no change.

1997), and physiological dependence similar to opioid dependence, in which AAS potentiates central endogenous opioid activity and withdrawal decreases endogenous opioids, leading to an acute hyperadrenergic syndrome (Kashkin and Kleber, 1989). Support for the similarity of AAS dependence to opioid dependence is limited in the literature. There are case reports indicating that AAS users are at risk for developing opioid abuse (Tennant et al, 1988). Kanayama et al (2009b) examined 5 naturalistic-type studies published between 1991 and 2005 that recruited AAS users from gymnasiums or the Internet and attempted to diagnose AAS dependence using the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) criteria of the American Psychiatric Association for substance dependence. They found that 30% of these study participants met DSM-IV criteria for noncyclic dependence, with an average age of onset of dependence in the late 20s (Johnson et al, 1989; Johnston et al, 2009; Kanayama et al, 2009a; Kanayama et al, 2009b). Kanayama et al (2009a) suggest that there are likely hundreds of thousands of men in their 30s and 40s who began use in high school and are currently dependent on AAS. Many more are likely to experience clinically significant side effects of AAS on fertility (Tennant et al, 1988; Kanayama et al, 2009a).

The understanding of how AAS affects spermatogenesis is complicated by several factors. The method used to obtain information is usually through naturalistic study design, with recruitment of AAS users from gymnasiums or the Internet. This method of recruiting users has inherent selection biases because some users may be more or less likely to disclose their abuse, as well as information bias if users choose to not disclose their use, side effects, and concurrent medications. Many abusers concurrently take antiestrogens, aromatase inhibitors, and human chorionic gonadotropin (hCG) to counteract the adverse effects of AAS and perhaps avert the detection of their use (Kanayama et al, 2009a).

Even though AAS are Schedule III drugs, they are easy to order over the Internet and easy to self-administer (Duchaine, 1981; Phillips, 1991). There is an extreme variability in the types, doses, combinations, and dosing schedules of AAS. Because a direct dose-response relationship between AAS and muscle growth exists (Bhasin et al, 1996, 2001), it is estimated that AAS users often take 600–5000 mg of AAS per week (Parrott et al, 1994; Pope and Katz, 1994; Wilson-Fearon and Parrott, 1999; Fudala et al, 2003; Parkinson and Evans, 2006). These doses are supraphysiologic in that they are 50–100 times greater than the 40- to 50-mg weekly production of testosterone by normal male testes (Reyes-Fuentes and Veldhuis, 1993).

Not only do the combinations and types of AAS vary widely, the administration and dosing schedules are just as variable. Typically, two or more types of AAS are taken simultaneously in blocks of 8–16 weeks, and doses are increased and then decreased over the course of the active block, termed ''stacking,'' ''cycling,'' and ''pyramiding,'' respectively (Lukas, 1993; Pope and Katz,

1994; Kanayama et al, 2003). The goal is to maximize both receptor binding and effect, avoid plateauing, avoid tolerance, and minimize the withdrawal symptoms of fatigue, loss of libido, and depressed mood.

Male fertility requires active spermatogenesis, which depends on Leydig cells secreting high levels of endogenous intratesticular testosterone. However, supraphysiologic levels of exogenous AAS actually exert negative feedback on the hypothalamic-pituitary-testicular axis and subsequently reduce FSH, LH, and intratesticular testosterone concentration. These hormonal changes can lead to azoospermia, oligospermia, testicular atrophy, hypogonadotropic hypogonadism, and an increased percentage of morphologically abnormal sperm with amorphous spermatozoa and defects in the head and center pieces (Table 6; Schurmeyer et al, 1984; Torres-Calleja et al, 2001; Bonetti et al, 2008).

Usually, spermatogenesis recovers spontaneously within 4–6 months after cessation of AAS (Knuth et al, 1989), timing that is similar to the recovery of spermatogenesis after the use of pharmacologic levels of testosterone for male contraception (Liu et al, 2006). However, recovery has been reported to take up to 3 years or longer (Schurmeyer et al, 1984; Turek et al, 1995; Menon, 2003). Reasons for the extended recovery time are not yet known but are likely due to the wide variety of combinations and types of AAS. Various clinical treatments have been prescribed to reestablish fertility (Gazvani et al, 1997). Human chorionic gonadotropin can induce spermatogenesis (Martikainen et al, 1986; Gill, 1998). Tamoxifen, an estrogen receptor blocker, when combined with hCG may alter gonadotropin secretion and improve spermatogenesis, as well as possibly stimulate endogenous testosterone production (Damber et al, 1989). Clomiphene citrate, a nonsteroidal antiestrogen most often used to initiate ovulation in women, has also been applied in a short course to stimulate normal sex hormone secretion in males by producing a gonadotropin surge (Guay et al, 1995; Tan and Vasudevan, 2003).

Although the combination of hCG and AAS can maintain spermatogenesis, there can also be a transient impairment on semen quality with abnormal and hypokinetic spermatozoa (Karila et al, 2004). Many users of AAS are concurrent abusers of hCG, antiestrogens, and aromatase inhibitors in order to counteract the hypogonadotropic hypogonadism and gynecomastia side effects of AAS, and to disguise and prevent detection of AAS abuse (Karila et al, 2004; Basaria, 2010). Human chorionic gonadotropin and antiestrogens are on WADA's 2009 list of prohibited androgens and androgen modulators. By stimulating endogenous testosterone production and preventing testicular atrophy, hCG and clomifene are concurrently abused by AAS users to avoid detection of exogenous testosterone (Kicman et al, 1990; Hoffman et al, 2009).

It is difficult to study AAS use and its side effects because of the variable dosing as well as the prevalence of selection and information biases in research design, because most AAS users are recruited from gymnasiums or through the Internet. Clinicians can look for increased libido, virilization, and bulk muscle with atrophic testes as signs of AAS use, but counseling patients can be difficult. Many are fearful to disclose their use of illegal substances and subsequently do not report side effects (Lloyd et al, 1996; Cohen et al, 2007). Pope et al (2004) interviewed 80 weightlifters, 54% of whom were current AAS users. Although 50% of those using AAS respected physicians with regard to their general medical knowledge, they did not regard the knowledge of the physician regarding AAS as any more reliable than that of their friends, Internet sites, or suppliers of AAS (Pope et al, 2004). Importantly, 56% of the users had never revealed their AAS use to a physician. Confounding variables such as premorbid attributes of AAS users or concomitant use of other substances also likely influence observed associations in the literature (Kanayama et al, 2009a). Furthermore, many drug abusers use multiple illicit medications. These medications are used because of their perceived desired effects and to prevent adverse effects caused by the primary abused drug or drugs. This makes interpretation of the literature complicated and often misclassifies adverse effects to one drug that may in fact be due to a coadministered illicit agent.

Conclusion

Illicit drug use is prevalent in our society and may adversely impact male fertility. Use of these illicit substances is often during reproductive years or during critical periods of testicular development. Illicit drug use affects the hormonal axis and causes impairments in semen analysis and functional sperm parameters. There are several notable limitations of our present understanding of the effects of illicit drugs on male fertility. Human studies are limited by their retrospective nature considering prospective studies are challenging to enroll because of the illegal nature of these substances and the fact that their dangerous side effects make human studies unethical. It is difficult to assess and control for multiple illicit drug interactions because many persons taking illicit drugs are often not just taking one type of drug, and interactions with other foods and drugs may affect the metabolism of an illicit drug. For example, AAS, opioids, and cocaine are metabolized via cytochrome p450, and thus inhibitors of this metabolic pathway could prolong the illicit drugs' side effects.

Also, interactions can occur as a result of the synthesis of pharmacologically active metabolites, as is the case with the concurrent ingestion of cocaine and alcohol, which produces cocaethylene, a cocainelike compound that enhances the toxicities of these substances (McCance et al, 1995).

Although estimates have been made regarding the prevalence of illicit drug use, it cannot be determined with accuracy how often illicit drug use leads to impaired spermatogenesis.

When evaluating infertility, it is important for clinicians to inquire about drug use, because use of illicit drugs is often not clearly evident to the clinician. If social history is positive for drug use, the clinician has the opportunity to coordinate treatment to improve reproductive function and initiate lifestyle modifications. The cornerstone to treatment is the cessation of drug use followed by a careful assessment of endocrine status.

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